Researchers report effective immune suppression therapy following traumatic brain injury

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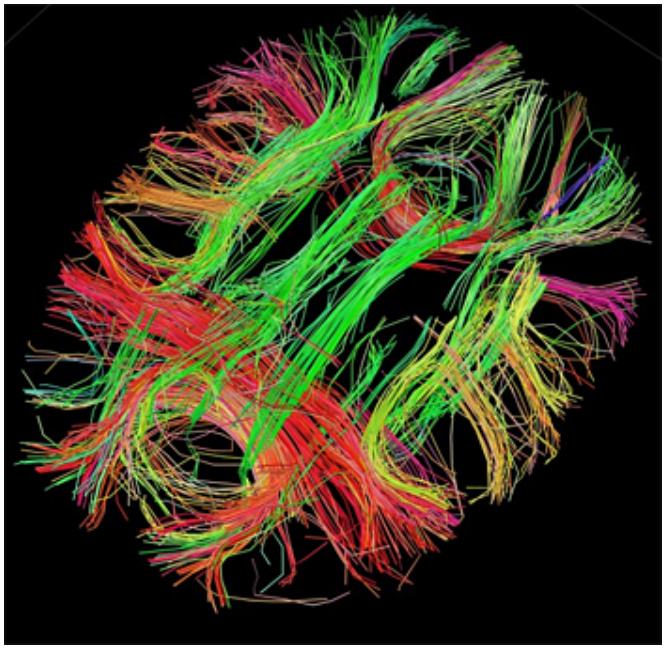

White matter fiber architecture of the brain. Credit: Human Connectome Project.

(Medical Xpress)—The growing awareness of traumatic brain injury (TBI) in professional, collegiate and amateur sports has resulted in legal pressures, media coverage and medical research related to the pathology of head injuries. The problem is particularly acute in contact sports such as U.S. football, but even lower-impact sports have produced examples of the disabilities induced by even minor head trauma.

The pathology of TBI is produced not only by the initial injury, but during the body's protective immune response. The body's complement system is an auxiliary, innate immune system that helps phagocytes and antibodies to clear pathogens. Unlike the adaptive immune system, the complement system is not adaptive, unable to produce counters to novel infections.

In the event of traumatic brain injury, complement is a key contributor to neuropathology and disability. Deployed to the site of injury to fight infections, the complement system's membrane attack complex (MAC) induces inflammation and inflammasome activation and causes lysis in brain cells. Thus, researchers view inhibiting MAC and preventing complement-mediated lysis as a goal in the prevention of TBI disability.

A group of researchers in the U.K. and the Netherlands have now collaborated on a study, published in the *Proceedings of the National Academy of Sciences*, describing an anti-complement agent that targets brain damage and promotes recovery in mice with traumatic brain injury. Crucially, the agent demonstrated effectiveness post-injury, implying the existence of a therapeutic window following head trauma for the prevention of secondary neuropathological effects and associated disability.

The researchers sought an agent that would inhibit MAC from inducing lysis while preserving its anti-infection properties. The complement inhibitor they used combined the so-called complement receptor of the Ig superfamily (CRI_g) with complement regulator CD59a. This construct was designed to inhibit MAC assembly only at sites of injury by targeting deposition of essential complement components C3bi and C3b, thereby suppressing detrimental effects of the complement system while maintaining its upstream anti-infection functions.

They report that the CD59-2a-CRI_g construct reduces posttraumatic neurologic disability and weight loss symptoms, which were monitored as an additional clinical outcome. The mice in the study

demonstrated a 50 percent reduction of the neurological severity score after four hours, by comparison with untreated controls. Further, the authors note that the construct reduces inflammation, mitochondrial stress and axonal injury after incidents of TBI. By inhibiting inflammosome activation post-TBI, it regulates secondary inflammatory processes that contribute to brain injury.

And importantly, as the injured mice were treated 30 minutes post-TBI, the authors suggest that a window exists for anti-complement therapy to be administered by emergency responders: "The data suggest a therapeutic window of opportunity for effective intervention after TBI to prevent secondary neurological damage, raising the prospect that such strategies may work when administered postinjury in humans, perhaps by first responders at the scene or in the ambulance, as currently happens with thrombolytics with a reported 4.5-hour window," the authors write.

More information: An anticomplement agent that homes to the damaged brain and promotes recovery after traumatic brain injury in mice. *PNAS* 2015 ; published ahead of print November 2, 2015, DOI: 10.1073/pnas.1513698112

Abstract
Activation of complement is a key determinant of neuropathology and disability after traumatic brain injury (TBI), and inhibition is neuroprotective. However, systemic complement is essential to fight infections, a critical complication of TBI. We describe a targeted complement inhibitor, comprising complement receptor of the Ig superfamily (CRIg) fused with complement regulator CD59a, designed to inhibit membrane attack complex (MAC) assembly at sites of C3b/iC3b deposition. CRIg and CD59a were linked via the IgG2a hinge, yielding CD59-2a-CRIg dimer with increased iC3b/C3b binding avidity and MAC inhibitory activity. CD59-2a-CRIg inhibited MAC formation and prevented complement-mediated lysis in vitro. CD59-2a-CRIg dimer bound C3b-coated surfaces with submicromolar affinity (KD). In experimental TBI, CD59-2a-CRIg administered posttrauma homed to sites of injury and significantly reduced MAC deposition, microglial accumulation, mitochondrial stress, and axonal damage and enhanced neurologic recovery compared with placebo controls. CD59-2a-CRIg inhibited MAC-induced inflammasome activation and IL-1? production in microglia. Given the important anti-infection roles of complement opsonization, site-targeted inhibition of MAC should be considered to promote recovery postneurotrauma.